REMARKS

Claims 1-4, 6-16, 18-25 and 28-36 are pending in the application and are at issue.

Claims 1-4, 6-16, 18-25, and 28-37 stand rejected under 35 U.S.C. §103 as being unpatentable over WO 97/03675 (WO '675) in view of WO 96/38131 (WO '131 and U.S. Patent No. 4,721,709 ('709). In view of the Declaration of Martha A. Kral (Kral Declaration) submitted concurrently with this amendment, and for the reasons set forth below, it is respectfully submitted that this rejection should be withdrawn.

In Amendment "B" filed on July 11, 2005, applicants provided a description of the present invention, and the benefits provided by the presently claimed invention. This description is reiterated below for the convenience of the examiner, and the attached Kral Declaration clearly shows surprising and unexpected results of the present invention and also supports the benefits described below with objective evidence from a comparison of the presently claimed formulations to formulations in the cited primary reference.

The present invention is directed to a pharmaceutical formulation, which exhibits unexpected and surprising results in therapeutic delivery of Compound (A) through enhanced dosage uniformity, stability, and bioavailability. As a result, the present invention achieves a rapid onset of a therapeutic effect, which has been identified as a problem involving the β-carboline (see specification, page 1, lines 16-19; page 2, line 24 through page 3; page 7, lines

21-28). The unexpected and surprising results of the present formulation are achieved because of (i) the presence of Compound (A) as a free drug comprising a particle size of less than about 40 microns *and* (ii) the presence and amounts of other important formulation ingredients, such as a water-soluble diluent, a lubricant, a hydrophilic binder, and a disintegrant. The present application specifically discloses that "the particle size of the active compound also has been found to enhance the bioavailability and handling of the present formulation" (see specification page 8, lines 14-23). The effects and importance of other formulation ingredients are also disclosed in detail, for example, at page 9, lines 24-33; and page 10, lines 16-23. Furthermore, the present invention provides a formulation having improved stability over prior formulations, in addition to improved dissolution and *in vivo* adsorption (page 12, line 32 through page 12, line 2). These advantages over compositions disclosed in WO '675 are demonstrated in the attached Kral Declaration.

Briefly, WO '675 discloses a method of treating male erectile dysfunction using Compound (A) and a tablet containing Compound (A), i.e., tablet formulations A.1., A.2., B.1., and B.2. at pages 12-15 of the specification. However, as stated by the examiner, WO '675 fails to teach or suggest use of a free drug form of Compound (A), the particle size of Compound (A), *or* the specifically claimed formulation, let alone all three features.

As stated above, the presently claimed formulations provide a stable composition that effectively

delivers the claimed compound (i.e., Compound (A)) *in vivo*. Because Compound (A) is a highly water-insoluble drug, its formulation into a pharmaceutical composition that effectively delivers the drug is not straightforward. As a result of applicants' investigation, a pharmaceutical composition that is surprisingly physically stable, and that demonstrates improved dissolution and *in vivo* absorption has been achieved.

The differences between WO '675 and the present claims are substantial. First, the presently claimed formulation contains Compound (A) as a free drug in a claimed particle size, whereas WO '675 fails to teach or suggest either of these features of Compound (A). These features, together with the other claimed formulation ingredients, provide the new and unexpected benefits achieved by the presently claimed invention described above.

In addition, the presently claimed formulations, as a whole, are substantially different from the formulations disclosed in WO '675. This is further illustrated by the Kral Declaration discussed below. The following table compares a composition disclosed in WO '675, and relied upon by the examiner, to the presently claimed compositions.

Ingredient	WO '675[1)]	Claim 1
1. Compound (A)	10% w/w	present
2. polyvinyl pyrrolidone (PVP)	30% w/w	present
3. polyethylene glycol (PEG)	10% w/w	not present
4. polysorbate 80	2% w/w	present (claim 3)
5. magnesium stearate colloidal silicon dioxide	0.5% w/w 0.5% w/w	present
6. croscarmellose sodium	5% w/w	present
7. microcrystalline cellulose	42% w/w	present (claim 2)
8. water-soluble diluent	not present	50-80% w/w

[1)] Formulation B.1. at page 13 of WO '675.

The compositions of WO '675 and claim 1 (or a claim depending therefrom) both include Compound (A), a wetting agent (e.g., polysorbate 80), a lubricant (magnesium stearate and colloidal silicon dioxide), croscarmellose sodium, and microcrystalline cellulose.

However, the compositions then greatly differ. For example,

(a) the composition of WO '675 contains PEG. Claims 1 and 6 recite a water-soluble diluent, including a polyol, which by definition does not include PEG. See the diluent examples in the specification (all of which are solids at room temperature), and see the definition of a "polyol" previously provided with Amendment "A."

(b) the composition of WO '675 contains 10% w/w PEG, which even if considered a water-soluble diluent, as stated by the examiner, is far below the 50-85% w/w recited in claim 1 for the water-soluble diluent.

(c) the composition of WO '675 contains 30% w/w PVP, whereas the present formulation contains a much lower amount of hydrophilic binder of about 1-5%

w/w. Furthermore, WO '675 fails to teach or suggest a cellulose derivative as the hydrophilic binder. Contrary to the examiner's statement, applicants did not previously argue that WO '675 does not teach PVP. As stated above, WO '675 does not teach a cellulose derivative.

In view of the above, WO '675 fails to teach the "same" pharmaceutical compositions containing the "same" active compound and excipients, as asserted by the examiner, and WO '675 fails to teach or suggest the present invention as a whole. Accordingly, it is submitted that the present invention as a whole would not have been obvious over WO '675.

The Kral Declaration is submitted to demonstrate the unexpected and surprising results of the presently claimed invention and to further demonstrate the differences between a presently claimed formulation and formulation examples disclosed in WO '675. As set forth in the Kral Declaration in paragraph 9, Example B1 of WO '675 is neither a workable nor a practicable formulation and process. Example B1 contains 10% PEG as a binder, which is known to potentially prolong tablet disintegration time. Such a thermoplastic granulation is used to prepare dosage forms that dissolve slowly, which negates advantages of the present invention, i.e., rapid dissolution for rapid onset of action and enhanced bioavailability. See Kral Declaration, paragraph 9.

Formulations of the present invention incorporating a water-soluble diluent, i.e., lactose monohydrate, together with a hydrophilic binder pro-

vided good granulation for compressibility (Kral Declaration, paragraph 16). This could not be accomplished using PEG as a water-soluble diluent, and the disadvantages of PEG in the formulation as applied to the present invention are discussed further in paragraph 9 of the Kral Declaration.

Examples A2 and B2 of WO '675 are addressed in paragraphs 10-13, 15, and 17-19 of the Kral Declaration. The Kral Declaration demonstrated that tablets prepared from Example A2 of WO '675 are extremely hard and failed to release an acceptable amount of the drug during dissolution (Kral Declaration, paragraph 13). Tablets made in accordance with Example B2 of WO '675 dissolved very quickly, but were too soft to maintain tablet integrity in further manufacturing steps (Kral Declaration, paragraph 15).

The Kral Declaration, at paragraphs 16-20, demonstrates that tablets prepared from a presently claimed formulation (a) overcome the problems associated with the tablets of WO '675 as stated above *and* (b) exhibit the unexpected and surprising benefits of tablet stability, a rapid therapeutic onset, and good bioavailability (paragraph 17). In particular, paragraph 17 of the Kral Declaration states how formulation changes employed by the present invention that were neither taught nor suggested by WO '675 produced tablets that overcame prior problems and provided unexpected and surprising results. These unexpected results are described in paragraphs 18 to 20 of the Kral Declaration with respect to tablet hardness (which helps maintain the integrity of the tablet for further

manufacturing processes) and dissolution rates wherein a present formulation releases the drug more quickly and more completely to provide a rapid onset of the therapeutic effect and enhanced bioavailability.

Moreover, in addition to the reasons set forth above and the unexpected results demonstrated in the Kral Declaration, the nonobviousness of the present invention is further demonstrated by claimed features that the examiner acknowledges are *not* disclosed or suggested in WO '675, i.e., particle size of Compound (A), percentages of ingredients, and amounts of drug in the tablet or capsule (see Office Action, page 3, lines 12-14). The examiner also made an erroneous assumption in reasoning by concluding that WO '675 teaches a free form of Compound (A) because WO '675 fails to disclose an imbedded form of Compound (A). This conclusive basis of rejection and reasoning cannot, without any support, be maintained because it is not in accordance with well-established standard of obviousness test. WO '675 is silent with respect to the form of Compound (A) in the formulation, and thus simply did not disclose this aspect of the present invention.

The secondary WO '131 and '709 references do not overcome the deficiencies of WO '675 for the reasons stated below.

WO '131 is directed to, *and limited to*, improving the bioavailability of poorly water-soluble drugs, like Compound (A), by forming a *coprecipitate dispersion*. WO '131 explains the problems associated with poorly water-soluble drugs in the free form, e.g., poor bioavailability, and teaches that solid disper-

sions of a poorly water-soluble drug may overcome these problems. WO '131 then discloses a coprecipitation technique that overcomes the problems associated with poorly water-soluble drugs in the free form and prior solid dispersions. See WO '131, pages 1-4.

Unlike the present invention, WO '131, therefore, teaches (a) the advantages of forming a coprecipitate, and (b) *avoiding* the free form of a poorly water-soluble drug, like Compound (A), in order to improve dissolution of the drug. WO '131 provides absolutely no teaching or motivation to utilize a free form of Compound (A) in a pharmaceutical formulation to achieve enhanced bioavailability and stability, but rather teaches away from using the free form of Compound (A) to achieve what has achieved by the presently claimed formulation. In fact, it is the problem encountered using a free form of a poorly water soluble drug that WO '131 addresses and attempts to solve.

Moreover, WO '131 discloses formulations that contain Compound (A) only as a coprecipitate, which again is substantially different from the presently claimed formulations. Therefore, contrary to the examiner's contention, the specific β-carboline coprecipitate compound taught in WO '131 is *different from* the presently claimed free form of Compound (A) in the claimed particle size. In addition, the examiner acknowledges at page 4 of the Office Action that WO '131 "fails to teach the claimed particle sizes," and further, WO '131 fails to suggest using the claimed particle size. Finally, the formulations disclosed in WO

'131 at pages 16-19 are substantially different from the presently claimed compositions as a whole.

The examiner contends that WO '131 "nowhere compares and teaches away from preparing a free drug formulation as opposed to the preferred co-precipitate." The examiner is referred to page 1, lines 3-8 of WO '131, which clearly states that the WO '131 invention relates to coprecipitates, and to *all* examples which utilize coprecipitates. WO '131 does not provide a comparison between a free drug form and a coprecipitate because it clearly states the disadvantages of the poorly water-soluble drug, e.g., Compound (A), and solves these problems by coprecipitation.

In view of the above, the cited references, alone or in combination, fail to provide a teaching or suggestion to modify and arrive at the presently claimed invention as a whole, and the modification would be successful in achieving unexpected and surprising results as stated in detail above. Accordingly, the present invention, as a whole, is not obvious over the cited references alone or in combination.

Seth et al. '709 also fails to cure the deficiencies of the combined teachings of WO '675 and WO '131. The '709 patent merely teaches fine particle size benzodiazepine drugs *adsorbed* onto a carrier. According to '709 patent, the critical feature of the Seth invention is directed to "the fine particle size of the adsorbed hydrophobic drug" (see column 6, lines 13-14). In addition, as stated by the examiner, the "method of Seth comprises the steps of providing dry

powder of the insoluble drug that is adsorbed onto a carrier" and "Seth teaches that the drug particles are closely associated with the carrier" (Office Action, page 4). This is in direct contrast to the presently claimed feature of a *free* particle form of Compound (A), which is *not* adsorbed onto a carrier. The '709 patent simply fails to teach or suggest a free form of the drug, but rather teaches the *necessity and criticality* of adsorbing the drug onto a carrier (see '709 patent, column 4, lines 44-52, for example).

The '709 patent also is addressed in paragraph 9 of the Kral Declaration. The declarant notes that as disclosed in the '709 patent (column 2, lines 13-17), micronized particles have the disadvantages of agglomeration, poor flow, and poor wetting. The '709 patent overcame these problems by *adsorbing* the micronized drug onto a pharmaceutical carrier. In contrast, the presently claimed invention employs micronized free drug *without* adsorbing onto a pharmaceutical carrier, which the '709 patent requires as critical to solving the problem. Moreover, the formulations provided in the '709 patent at columns 9 and 10 are substantially different from the claimed formulations as a whole, and provide no suggestions with respect to modifying the formulation to arrive at the presently claimed formulation as a whole. The '709 patent, therefore, not only fails to teach or suggest a free form of a drug, but also fails to teach or suggest any formulations or formulation modifications that would help overcome the deficiencies of WO '675 and WO

'131, taken alone or in combination, to render the present claims obvious.

Furthermore, as previously stated, the examiner misapplies applicants' incorporation of U.S. Patent No. 4,605,517 in the present specification ('517) by reference. As specifically stated in the present specification at page 8, lines 28-32, the '517 patent is incorporated by reference *merely* for the purpose of instructing persons reading the present specification how to measure particle size, and, thus, the '517 patent is not referenced for a method of preparing the present formulations. Preparation of the present formulations is illustrated in the examples of the present application, and, thus, do not rely upon the method of U.S. Patent No. 4,605,517.

In summary, for the reasons stated above, and because of the unexpected results demonstrated by the Kral Declaration, the present invention, as a whole, is neither taught nor suggested by any of the cited references, alone or in combination. Accordingly, it is respectfully submitted that the rejection under 35 U.S.C. §103 should be withdrawn.

Claims 1-4, 6-16, 18-25, and 28-36 also stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,821,975. In view of the terminal disclaimer filed concurrently with this amendment, it is submitted that this rejection has been overcome and should be withdrawn.

In summary, it is submitted that the present claims are in a form and scope for allowance. An early

and favorable action on the merits is respectfully requested.

Should the examiner wish to discuss the foregoing, or any matter of form in an effort to advance this application toward allowance, the examiner is urged to telephone the undersigned at the indicated number.

Respectfully submitted,

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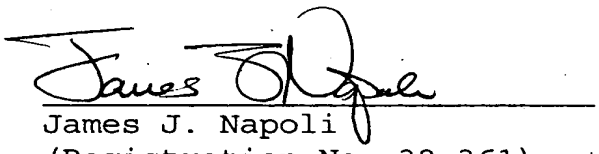
By 

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December 21, 2005